Docket No. 833970 0002 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: STROBEL et al.

Serial No.: 09/801,908 Group Art Unit: 1614

Filed: 03/09/2001 Examiner: Henley, Raymond J. III

For: KETOPROFEN POWDER FOR ORAL USE

DECLARATION OF MICHAEL A. STROBEL UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael A. Strobel, reside at 1479 Dixon Path, Northfield, MN 55057, hereby declare and state as follows:

1. I am one of the inventors of the above-identified pending U.S. patent application.

2. I am a registered Doctor of Veterinary Medicine in the State of Minnesota.

3 I am a 1982 graduate of the University of Minnesota with a Doctor of Veterinary Medicine degree. I also have been granted a Master's of Veterinary Medicine degree from the same institution. Prior to that, I attended the University of Minnesota and Mankato State University, Mankato, Minnesota, for my undergraduate degree studies.

4. Upon graduation from veterinary school, I joined Cannon Valley Veterinary Clinic and have been working here since that time.

5. The claimed invention in our above-identified pending application is directed to a method of forming a palatable, stable, and safe solution of ketoprofen and an oral base in water for use in mass medicating animals.

6. I have reviewed and studied the Office Action dated November 6, 2002 and the basis for the Examiner's Rejection under 35 USC §103 in view of Dondi et al. (U.S. Patent No. 5,624,682).

7. I believed there to be precipitation problems in using the Dondi et al reference in the manner taught by the claimed invention so I prepared and ran the five (5) examples taken from Dondi et al. to confirm my belief.

8. An experiment was undertaken to validate the following examples and determine the compatibility in larger volumes of water. I followed each of the following examples exactly as disclosed and mixed the corresponding mixture with 2 gallons of distilled and 2 gallons of tap water to see if the product would stay in solution and mix to a clear solution as occurs with our formulation of ketoprofen and sodium bicarbonate.

EXAMPLE 1

Formulation of soft ketoprofen capsules of 25 mg each

5000 soft gelatin capsules, each of which contains 25 mg of ketoprofen, were formulated with the following ingredients:

Gelatin per capsule	g	460.0
Glycerol	g	140.0
Purified water	g	330.0
Ketoprofen	g	125.0
PEG 600	g	625.0
Ethanolamine	g	28.1

The formulation of the gelatin shell used for preparation of the soft capsules is not in itself a part of the present invention, since this is already known. In general, these shells are formulated by companies which specialize in the production of soft gelatin capsules.

The formulation is explained below in broad outline with the sole purpose of providing a complete description of the invention. The gelatin is mixed in the abovementioned amount with glycerol and purified water in the amounts stated, the mixture being heated at 30.degree. C. for 3 hours, with constant shaking. After deaeration under reduced pressure, the solution thus obtained is maintained at a temperature of 50.degree. C. until the layer for the shell is prepared. As is known to the expert, other substances can be added to this solution where this is considered necessary, such as, for example, propylene glycol, sorbitol, preservative and dyestuffs. Thereafter, the ketoprofen is dissolved in PEG 600 with the addition of ethanolamine, in the abovementioned amounts, and the mixture is shaken until a transparent solution is obtained: in this manner, the constituents of the pharmaceutical formulation of the invention have a form appropriate for encapsulation. The individual capsules, each of which contains 25 mg of ketoprofen, are then formulated by encapsulating 156 mg of the solution described above in a manner known per se.

EXAMPLE 2

Formulation of soft capsules having in each case 50 mg of ketoprofen

2500 soft capsules which each contain 50 mg of ketoprofen were formulated in accordance with the description in Example 1, but using 312 mg of ketoprofen solution, instead of 156 mg.

EXAMPLE 3

In accordance with the process described in Example 1, 125 g of ketoprofen are dissolved in 625 g of PEG 400. The pH of the solution is established with 135 g of 50% strength DL-lysine, and 5000 soft capsules having in each case 25 mg of ketoprofen are formulated in accordance with Example 1.

EXAMPLE 4

In accordance with the process described in Example 1, 125 g of ketoprofen are dissolved in a mixture of 400 g of PEG 600 and 125 g of PEG 400. The pH of the solution is corrected with 27.9 g of ethanolamine, and soft capsules are formulated by encapsulating 156 mg of the solution thus prepared in each, in which case the dosage will be 25 mg of therapeutically acting substance per capsule, while 312 mg of the same solution must be encapsulated for formulation of capsules having in each case 50 mg of ketoprofen.

EXAMPLE 5

In accordance with the process described in Example 1, 125 g of ketoprofen are dissolved in a mixture of 600 g of PEG 400 and 25 g of glycerol. 28 g of ethanolamine are added and encapsulation is carried out in accordance with the conditions described in Example 1, corresponding to a dosage of 156 g or 312 g of the solution thus prepared.

The results of these experiments are as follows:

Example 1through 5: I performed this with and without the gelatin in the formulations since it is described as not being essential. The result was an immediate precipitation reaction when mixed at a ratio of greater then 0.5 water to 1 part of the formulation. The amount of precipitate became steadily greater as the amount of water increased. Heating to 120 degrees Fahrenheit did not improve the solubility. The precipitation was greater when the gelatin was not included but occurred with both formulations at the concentrations consistent with our pending application. This occurred with all the example formulations and would severely limit their use as a water based carrier system for ketoprofen.

9. In conclusion, it is my opinion based on the data and results of the examples conducted above, that Dondi et al. does not teach or suggest to one of ordinary

skill in the art a method of forming an oral, palatable, stable, and safe solution of ketoprofen and an oral base in water for use in mass medicating animals, i.e., the claimed invention in our above-identified pending application.

10 In fact, the attempted use of the teachings of Dondi et al. would destroy the intended benefits of our claimed invention as a result of the precipitation problems that take place. Dondi et al. was clearly designed for soft capsule usage and not for dispersal with ketoprofen and an oral base in a water solution.

11. Aside from the claimed invention of our pending application, I know of no other commercial or other experimental process that is oral, palatable, stable, and safe in the mass medication of animals with ketoprofen.

11. I further declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 4/5/03

Dr. Michael A. Strobel DVM/MS